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10/069,180

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,180	02/15/2002	Shigenori Ohkawa	2628 USOP	1643
7590	08/03/2004		EXAMINER	
Mark Chao Takeda Pharmaceuticals North America Inc Suite 500 475 Half Day Road Lincolnshire, IL 60069				MCKENZIE, THOMAS C
				ART UNIT
				PAPER NUMBER
				1624
DATE MAILED: 08/03/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.	10/069,180	Applicant(s)	OHKAWA ET AL.
Examiner	Thomas McKenzie, Ph.D.	Art Unit	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

1) Responsive to communication(s) filed on 03 June 2004.  
2a) This action is **FINAL**.      2b) This action is non-final.  
3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

4) Claim(s) 1-19,25-28,33 and 34 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
5) Claim(s) 1-16 and 18 is/are allowed.  
6) Claim(s) 17,19,25-28,33 and 34 is/are rejected.  
7) Claim(s) \_\_\_\_\_ is/are objected to.  
8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

9) The specification is objected to by the Examiner.  
10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) All    b) Some \* c) None of:  
1. Certified copies of the priority documents have been received.  
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

1) Notice of References Cited (PTO-892)  
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
    Paper No(s)/Mail Date 3/14/03.

4) Interview Summary (PTO-413)  
    Paper No(s)/Mail Date. \_\_\_\_\_.  
5) Notice of Informal Patent Application (PTO-152)  
6) Other: \_\_\_\_\_.

**DETAILED ACTION**

1. This action is in response to amendments filed on 6/3/04. Applicant has amended claims 17, 19, 25-28, 33, and 34. Claims 17, 19, 25-28, 33, and 34 were previously rejected. Claims 1-16 and 18 were designated as containing allowable subject matter. There are twenty-five claims pending and twenty-five under consideration. Claims 1-17 are compound claims. Claim 19 is a composition claim. Claims 25-28, 33, and 34 are use claims. Claim 19 is a method of synthesis claim. This is the third action on the merits. The application concerns some furo[2,3-f]indole compounds, compositions, and uses thereof.

***Information Disclosure Statement***

2. Applicants' cooperation supplying a copy of the IDS of 3/14/03 is appreciated. The IDS has been scanned and a signed copy enclosed.

***Response to Amendment***

3. Applicants' amendments concerning the structures of the claimed prodrugs as amino and hydroxyl derivatives overcomes both the indefiniteness rejection made in point #5 of the previous office action and the how to synthesize rejection made in point #7. Applicants' argument that claim 28 is not drawn to therapy but rather to simple inhibition of lipid peroxidation is persuasive. Thus the enablement rejection to that claim alone, made in point #8 of the previous office action is withdrawn. Applicants' deletion of "preventing" from claims 25-28 overcomes the enablement rejection made in point #9.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 19, 25-28, 33, and 34 remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making prodrugs generally. The specification does not enable any person skilled in the arts of synthetic pharmaceutical chemists and metabolism, to use the invention commensurate in scope with these claims. “The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The issue is the determination of any of Applicants' claimed prodrug derivatives, is in fact, a prodrug.

a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate

is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting passes the threshold of undue experimentation. Thus, a large quantity of experimentation is necessary. b) There is no direction in the specification to the determination of whether a compound is a prodrug nor is there any direction as to possible structures of such compounds. c) There is no working example of a prodrug of a compound formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetics of substances in the human body.

e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard

pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that “extensive development must be undertaken” to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. g) The lack of predictability in finding prodrugs was discussed above. h) The breadth of the claims includes all of the hundreds of thousands of compounds of the formula given in claim 1 as well as the thousands of potential prodrug derivatives of each compound embraced by claim 17. Thus, the breadth of the claims is huge.

MPEP 2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” Reconsideration of all the factors discussed above dictate that conclusion is still be made here. Thus, undue experimentation will be required to determine if any particular amine, alcohol, or carboxyl derivative is, in fact, a prodrug.

Applicants point to the passage in the specification from where their new amendments come, but make no arguments about the experimentation required for determining if the derivatives are prodrugs or are not.

5. Claims 25-27 and 34 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cranial trauma, does not reasonably provide enablement for treating cerebovascular impairment, dysuria, urinary incontinence, restenosis, or neurodegenerative diseases. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above. a) Determining if any particular claimed compound would treat any particular cardiovascular, neurodegenerative, urinary, or restenosis disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large quantity of experimentation. b) There is a *single in vitro* assay described, drawn to inhibition of lipoperoxidase from brain homogenates, in the passage spanning line 22, page 188 to line 5, page 190 with data for two species but it is unclear if this assay is correlated to clinical efficacy for treatment of all the

claimed diseases. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in lipoperoxidase inhibitors is discussed by Delanty (Arch. Neurol). The treatment of traumatic CNS injury with an inhibitor of lipoperoxidase production is found in the third complete paragraph, second column page 1268. The lack of clinical efficacy for stroke, neurodegenerative diseases, AIDS, and epilepsy with such inhibitors is found in the passage spanning pages 1267 to 1269. With reference to claim 26, Applicants should note the first sentence of the abstract of Solin (Kidney Int.), "little is known of their significance and respective scavenger systems in human glomerular diseases". Both dysuria and urinary incontinence are glomerular diseases.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1. In addition the term "neurodegenerative disease" covers a broad array of different

disorders that have different modes of action and different origins. The term covers such diverse disorders as Alzheimer's Disease; Parkinson's Disease; ALS and variants such as forms of ALS-PDC; Gerstmann-Straussler-Scheinker Disease (GSS); Pick's Disease; Diffuse Lewy Body Disease; Hallervordon-Spatz disease; progressive familiar myoclonic epilepsy; Corticodentatonigral degeneration; progressive supranuclear palsy (Steele-Richardson-Olszewski); Huntington's disease; more than a dozen dementias collectively called "frontotemporal dementia and Parkinsonism linked to chromosome 17" (FTDP-17); Tourette's syndrome; Shy-Drager syndrome; Friedrich's ataxia and other spinocerebellar degenerations; Olivopontocerebellar atrophy (OPCA); spastic torticollis; Striatonigral degeneration; various types of torsion dystonia; certain spinal muscular atrophies, such as Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander; Hereditary spastic paraplegia, Primary lateral sclerosis; peroneal muscular atrophy (Charcot-Marie-Tooth); Creutzfeldt-Jakob Disease (CJD); Hypertrophic interstitial polyneuropathy (Dejerine-Sottas); retinitis pigmentosa; Leber's Disease; and Hypertrophic interstitial polyneuropathy. These exhibit a very broad range of effects and origins. For example, some give progressive dementia without other prominent neurological signs, such as Alzheimer's disease, whereas other dementias have such signs, such as Diffuse Lewy Body Disease. Some give muscular wasting

without sensory changes, e.g. ALS, and some do have the sensory changes such as Werdnig-Hoffmann. Some are abnormalities of posture, movement, or speech, such as Striatonigral degeneration, and other are progressive ataxias, such as OPCA. Some are linked to tau mutations, such as Alzheimer's disease and FTDP-17, and other such as Parkinson's clearly do not. Some affect only vision such as retinitis pigmentosa. Even within those that fall into the same category of effects, there are often striking differences. For example, Alzheimer's disease and Pick's disease both give progressive dementia without other prominent neurological signs. However, the characteristic Alzheimer's neurofibrillary tangles are not seen in Pick's Disease, which has straight fibrils, as opposed to the paired helical filaments of Alzheimer's disease. Pick's Disease gives lobal atrophy, not seen in Alzheimer's disease. There are differences in origins, even with what little is known. Thus, among progressive dementias, CJD is definitely caused by an infectious agent; so far as can be determined, this is not so for Huntington's disease. Even among the hereditary disorders, the origins are different. Thus, FTDP-17 comes from chromosome 17, Huntington's disease from 4, and the neurodegenerative disorder that people with Down's syndrome develop later in life is presumably connected in some way to 21.

The great majority of these have no treatment at all, and of those that do, none or virtually none have been treated with such inhibitors as are disclosed here. The great diversity of diseases falling within the “neurodegenerative disease” category means that it is contrary to medical understanding that any agent (let alone a genus of trillions of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Further, what little success there has been does not point in this direction. Thus, what very few treatments that the massive research effort on Alzheimer’s disease has produced are means of providing acetylcholinesterase inhibition, unrelated to the mechanism of action in this case. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here and undue experimentation will be required to practice Applicants’ invention.

Applicants point to five scientific articles in support of their treatment claims to these four different diseases. This is not persuasive. A cursory review of these references fails to reveal any use of any substance to treat any disease. Applicants fail to point to any specific passages in these numerous and lengthy references that support this alleged clinical correlation. For example, Braugler (Free Radical Bio. & Med.) does not discuss the pharmaceutical treatment of any disease. Parekh (J. Oncology) presents the results of a study of using vitamin E in a rabbit model of bladder obstruction. Is Vitamin E an inhibitor of lipoperoxidase release, as are Applicants compounds? Were Applicants compounds ever tested in this rabbit assay? Is this rabbit assay predictive of human clinical efficacy? Jeremy (J. Card. Surg.) reviews oxidative stress and cardiovascular disease. This review does not even mention Applicants' lipoperoxidase release assay. What does the superoxide anion mentioned by Jeremy (J. Card. Surg.) have to do with lipoperoxidase? What has only of this to do with restenosis, which is the subject of the present claim 27? Dichter (Acta neurol. Scand.) in the last paragraph on page 150 writes, "[c]linical trials of putative antioxidants have been performed in recent years with mixed results". How does this provide enablement for treatment of all neurodegenerative diseases, as presently claimed? Were these clinical trials done with compounds active in Applicants' lipoperoxidase release assay? On page 148, a Vitamin E

analog, active as a scavenger of superoxide, is reported effective in the treatment of Alzheimer's. Do all such superoxide scavengers show that efficacy? Do some or only a few? Do Applicants' compounds scavenge superoxide? If so, where is the data? Jenner (Ann. Neurol.) reviews Parkinson's disease and oxidative stress. However, nowhere does this review state that inhibitors of oxidative stress have ever shown clinical efficacy for the treatment of PD. In fact in the conclusion Jenner (Ann. Neurol.) states that l-DOPA is the best drug for the treatment of PD. How does this provide enablement for Applicants' compounds ability to treat PD?

*Allowable Subject Matter*

6. Claims 1-16 and 18 remain allowed.

*Conclusion*

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date

of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

9. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact Mukund Shah SPE of 1624 at (571)-272-0674.



Thomas C. McKenzie, Ph.D.  
Patent Examiner  
Art Unit 1624

TCMcK/me